last line, delete in its entirety.

Claim 8, line 2, change "NF-κB decoy" to --nucleotide--.

Claim 9, lines 1-2, change "NF-κB decoy" to --nucleic acid of--.

--10. (Amended) A method for [therapy and prophylaxis] treatment and prevention of NF-κB-associated disease which comprises administering to an animal an effective amount of [an NF-κB decoy to a mammal] a nucleotide that binds to the NF-κB chromosomal binding site and antagonizes NF-κB-mediated transcription of a gene located downstream of said binding site.--

REMARKS

Claims 1-16 remain active in the application. Undersigned counsel thanks Examiner McGarry for a discussion of this case, summarized below. Favorable reconsideration is requested.

The present invention relates to a pharmaceutical composition for treatment of NF-κB-associated diseases. NF-κB is a heterodimer protein which acts as a regulation factor in the transcription of cytokines, such as IL-1, IL-6, IL-8, and adhesion factors such as VCAM-1 and ICAM-1. Production of these cytokines and adhesion factors causes damage which is associated with ischemic diseases, inflammatory diseases, autoimmune diseases, cancer metastasis and others. The present invention is a DNA that specifically antagonizes the NF-κB binding site of the chromosome, making it more difficult for the NF-κB protein to attach itself to the NF-κB binding site thereby preventing transcription of the genes located downstream. (See page 2, first paragraph of the specification).

Claims 1-9 are rejected under 35 U.S.C. §112, first paragraph; a written description

rejection.

The Examiner asserts that the claims should be limited to the exemplified sequence SEQ ID NO:1. However, the claims have been amended to recite functional language that clarifies the point that the composition contains a nucleotide which binds to the NF-κB chromosomal binding site. Furthermore, the nucleotide sequence of NF-κB binding site was published. Lenardo et al, Cell Vol. 58, 227-229 (1989), (submitted herewith). The purpose of the written description requirement is to ensure that the claims cover subject matter that was contemplated at the time of filing, and relates to the prohibition against new matter. In this case one can see that the Applicants did contemplate using DNA which binds to the NF-κB binding site of the chromosome to block NF-κB-mediated transcription of downstream cytokines and adhesion factors (paragraph bridging pages 1 and 2). Furthermore, the phrase "NF-κB binding site of the chromosome" is a complete description (to a person of skill in the art) of the DNA sequence of interest on the chromosome, as shown by Lenardo et al.

Claims 7, 9 and 17-23 are rejected under 35 U.S.C. §112, second paragraph. These rejections have been overcome by appropriate amendment.

Claims 17-23 are rejected under 35 U.S.C. §101 for being non-statutory "use" claims. These claims have been cancelled. The same subject matter is covered by the method claims.

Claims 1-6 and 8-16 are rejected under 35 U.S.C. §112, first paragraph on grounds that the specification is not enabling for the broad range of NF-κB decoys or for treating or preventing a broad range of diseases. As now presented, the claims are directed to "treatment and prevention" rather than prophylaxis. The term "prevention" should be acceptable in this case because it refers to the drug's mechanism of action, i.e., it blocks transcription of cytokines, which do the damage in NF-κB associated diseases. Particularly in view of the

fact that the NF-κB decoy is now claimed in functional terms and clarifies the role of the NF-κB chromosomal binding site sequence.

Furthermore, *in vitro* and *in vivo* data in the specification using SEQ ID NO:1 demonstrates that DNA which binds to the NF-κB chromosomal binding site does indeed antagonize transcription of downstream genes. Thus, a person of skill in the art would accept the assertion that the claims are enabled.

Claims 1-8 are rejected under 35 U.S.C. §102(a) over Russell et al, while Claim 9 is rejected under 35 U.S.C. §103(a) over Russell et al in view of Stull et al.

WO 95/12415 relates to a composition and method for modulating gene expression of a vascular cell adhesion molecule. An object of the invention was to provide an oligonucleotide diagnostic and therapeutic composition and method for modulating expression of genes associated with disease states implicating vascular cell adhesion molecules, particularly VCAM-1. A further object was to provide oligonucleotides which interact with one or more transcription factors to effect such modulation (page 5, lines 3-10). ICAM-1 and E-selectin were identified as being other adhesion molecules and NF-κB, GATA, Ap-1, Sp-1, Ap-2, interferon response factors, octamer transcription factor and NF-ELAM1 were exemplified as being transcription factors (page 7, lines 4-6 and etc.) WO 95/12415 only disclosed that oligonucleotides having a nucleotide sequence which is identical to a portion of the above transcriptional regulatory factors binding sequence would inhibit expression of adhesion molecules in the cell. This information does not suggest that an NF-κB decoy could be used for treatment of NFκB associated disease, nor is that likely the composition disclosed in the reference actually have the function recited in the present claims.

The Applicants invention relates to a composition which antagonizes NF-κB-mediate transcription of a gene located downstream of the NK-κB binding site. Our invention is the first one showing that an NF-κB decoy can be used to treat the various diseases associated with NF-κB in animals.

Applicants submit that the case is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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